ISSN: 3079-3319

Falcons Journal of Advanced Research

Volume: 03, Issue: (01), Article ID: FJAR-VOL3-01-26001A

Immunological Strategies Against Antimicrobial Resistance: Emerging Solutions in Veterinary and One Health Frameworks

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Abstract

The ever-increasing risk of antimicrobial resistance (AMR) is a major concern to worldwide health and veterinary medicine is a key factor in its growth and its solution. This chapter dwells on the cutting-edge immunological measures designed and implemented in the fight against AMR in animal wellbeing. It highlights the integrative measures of using the traditional veterinary-based practices, alongside novelty Immunotherapeutics such as vaccines, monoclonal antibodies, immunomodulators, and host-directed structures. The chapter explains the ways that can be used to minimize antibiotic dependency by taking advantage of the developments in the field of immunology, including the knowledge of the innate and adaptive immunities as well as microbiome-immune environment communication and pathogen- specific tactics of immunoreaction. Further, it emphasizes the relevance of One Health approach in planning sustainable and effective immunological interventions considering the health of animals, people, and the environment. Seeking to offer in-depth review of the ongoing struggle against AMR to achieve animal welfare and human health using immunological tools, this chapter can be thought of as a compilation of case studies and the latest research describing the movement towards the evolution of combating AMR in veterinary practice.

Keywords: *Antimicrobial Resistance, Immunomodulators, Vaccines, Immunotherapeutics, One health, Veterinary medicine*

Received: ***October 07, 2025*** *Accepted:* ***January 08, 2026***

How to Cite this Paper: Rehman, A., Naveed, F., Malik, Z., Zafar, F., Ali, Z., Munazza, M., Perveen, S., & Zafar, S. (2026). Immunological strategies against antimicrobial resistance: Emerging solutions in veterinary and One Health frameworks. *Falcons Journal of Advanced Research, 3*(1), 38-53. https://doi.org/10.63287/690241

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1. INTRODUCTION

As a primary challenge to global health, antimicrobial resistance (AMR) stems from an ancient evolutionary trait. This inherent ability to resist treatments allows bacteria to survive and thrive despite environmental changes. Intrinsic antimicrobial resistance is a feature of pathogenic, as well as, nonpathogenic microorganisms, as it is a necessity for the survival and evolution of the bacteria in such a complex environment (Sommer, M. O et al.,2010). The AMR menace is largely a result of overuse and misuse of antibiotics, which are prescribed largely unevenly, unnecessarily or by unqualified providers. Also, the anti-microbial therapy in animals (food and companion animals and exotic species) is responsible for selection and spread of resistant bacteria with a high degree of significance. (Von Wintersdorff et al.,2016). AMR in bacteria is the phenomenon of a bacteria not responding to standard doses of the latest clinically relevant antimicrobial drugs (Ganguly NK et al.,2011).

This was something of a surprise even to the science community, because as early as 1945 when Sir Alexander Fleming received his Nobel Prize, he warned of the danger that bacteria could develop resistance to antibacterial agents (Guidance for Industry, 2010). It was not long before reports of the wonder drug itself failing to be efficacious (Abraham EP et al., 1940). This was the beginning of dictating the failures of other therapeutic drugs against infectious agents that subsequently emerge and known as drug resistance, AMR or antibiotic resistance, and question the utility of contemporary therapeutic regimens. Yet indiscriminate use of disinfectants and antibiotics has resulted in global health problems never before imagined. This problem emerged when bacteria began producing genes enabling resistance to antibiotic residue. Resistance genes facilitate the spread of infections in different environments, thereby limiting the treatment options for infectious diseases, causing increased morbidity and mortality as a high number of resistant bacteria are proliferating in humans and animals.

The appearance, duration, and transmission of drug-resistant microbes are one of the significant challenges of modern medical practice and public health (Leung et al. 2011, Laxminarayan et al. 2013). Internationally, the danger and burden of AMR are familiar. For instance, antibiotic-resistant organisms lead to some 33,000 deaths per year in Europe and to 4.95 million deaths, worldwide, many of them resulting in EUR 1.5 billion per year of health system costs and productivity losses (European Commission. EU Action on Antimicrobial Resistance et al.,2023). Estimates indicate that AMR related mortality is highest in sub-Saharan Africa and lowest in Australasia. Notably, methicillin-resistant *staphylococcus aureus* (MRSA) alone was linked to half a million deaths. Furthermore, a group of six key pathogens-including *E. coli* and *K. pneumoniae* were each responsible for 50,000 to 100,000 deaths (Murray et al., 2019).

As a multifaceted threat, AMR necessitates a 'One Health' response that unites human, animal, and environmental health sectors (Roinson et al., 2016). While international mitigation efforts highly priotze this integrated approach, current actions primarily target antibiotic reduction in livestock. Research shows this effectively lowers resistance in animals, though the impact on human health is less pronounced (Hoelzer et al., 2017). Moving forward, the challages lies in aligning the conflicting interests of various stakeholders to reach a consensus on AMR measurement, infection control, and regulatory policies.

The biggest dangers to world health today is antimicrobial resistance, which jeopardizes the efficacy of life-saving therapies in human and animal populations. The extensive use and abuse of antibiotics in agriculture, companion animals, and cattle in veterinary medicine and interrelated ecosystems hastens the emergence and spread of resistant infections across species and environmental boundaries. Immunological approaches, including vaccines, immunomodulators, monoclonal antibodies, and host-directed treatments, are becoming more popular as potential substitutes or supplements to conventional antibiotics. These cutting-edge solutions, which are framed within the One Health approach which acknowledges the interconnection of human, animal, and environmental health strive to lessen the need for antibiotics while boosting immunological resilience and disease prevention. Investigating these novel immunological therapies provides a vital route to long-term management of infectious illnesses and AMR reduction in veterinary and international health systems.

Alternatives to antibiotics encompass a diverse range of products, including vaccines, antibiotics, pattern receptors,

and probiotics. This pipeline also extends to bacteriophages, peptides, phytochemicals, metals and antimicrobial enzymes. (Pew Charitable trusts et al., 2020).

In addition to sanitation, vaccines and AMs have provided the cornerstone for advancements in public health. Indeed, with introduction of antibiotics and other AMs, AMR seems to have been accelerated. The current state of AMR has made it clear that it is one of those paradoxes, wherein the free ability to use conflicts with the desperate need for use, and a united action in all levels - multi-sectoral - integrated action is needed to identify and undertake national and global level action. On-going inappropriate use and excessive use of these drugs in food animals drives the occurrence of resistant bacteria which can then be transmitted to humans either following ingestion of food, handling of animals or through the environment (Angulo, F.J et al.,2005). Differences in how vaccines and antibiotics work mean that the chances of resistance evolving because of vaccination is also far less likely. Vaccines are best suited for acting prophylactically – before pathogens have a chance to reproduce and disseminate throughout various tissues. This is essential to decrease the risk of evolving a drug resistance through mutations in the pathogen genome (Bagnoli, F., et al. Chief among these could be the vaccines that could help confine the spread of resistant bugs and the accompanying AMR. Vaccines are important achievements in the history of immunology, particularly because prophylaxis therapy of patients internationally speeds up increase of their life expectancies (Costanzo, M. et al.,2022).

1.1 Objective

The aim of this study is to evaluate the role of immunological strategies, including vaccination, immunomodulation, and host-directed therapies, in enhancing disease resistance in animals and reducing the reliance on antibiotics in veterinary medicine. It also seeks to examine the effectiveness of integrative and One Health approaches that combine veterinary practices, antimicrobial stewardship, and environmental management to prevent the adaptation and spread of antimicrobial resistance across animal, human, and ecosystem interfaces.

2. THE BURDEN OF AMR IN VETERINARY MEDICINE

Antimicrobial resistance has become the most pressing global health issues, and interventions to combat AMR, such as antimicrobial stewardship, infection prevention, and biosecurity programs, investment in research and development (R&D), and increased monitoring and surveillance, have been more widely adopted (T.A. Ghebreyesus et o l.,2019). As the social and economic burdens of antimicrobial resistance become clearer global efforts to secure funding and take decisive action have accelerated. The costs of AMR have become stronger drivers for both research and policy to address the problem. Over the last 20 years measurements have expanded from attention to bugs, to attributable deaths, to economic costs. WHO (2001) The World Health Report 2006: working together for health - The 2001-2010 strategy. 2001)

AMR started with the 1998 WHA declaration (World Health organization. 1998). Both clinical and economic burden were explicitly highlighted across these calls to action, but the pathogens coded for in laboratory surveillance and reporting was the recommended measure.

Antibiotics are used in food-producing and companion animals for treatment, meta phylaxis, prophylaxis, and growth promotion. Antimicrobials are frequently used in food animals, including poultry, swine, and cattle, as medicated feed or water to prevent disease and improve growth performance. The author stresses that more judicious use, regulation, and surveillance are required to control these risks and conserve the efficacy of available antimicrobials (Prescott, 2008). Compared to others, antibiotics were classified into two groups: CIAs and others. For the present report, CIAs are defined according to the WHO classification of antibiotics (WHO 2011) in relation to their importance in human medicine and are composed of (fluoro)quinolones, third- and fourth-generation cephalosporins, macrolides and glycopeptides. In addition to their high consumption with thousands of tones used worldwide. Antibiotics are employed in most, if not all, countries to combat animal disease and to preserve animal health and are used in the feed to promote animal growth and feed efficiency. Adverse effects of antibiotic fand environmental Nimal secretions, mainly in manure and urine of the animals from drinking water and feed, to get fed will be their way, to soil and the environment contamination (Spaepen KR et al., 1997).

FJAR Falcons Journal of Advanced Research
ISSN: 3079-3319
Volume: 3,
Issue:(01)
Nov 25 - Jan, 2026

Animal health, food security, and public health are all threatened by the burden of antimicrobial resistance (AMR) in veterinary medicine. Farmers and veterinary systems are severely strained financially because of resistant bacterial infections in livestock and companion animals, which can cause greater morbidity and death, extended illness, decreased output, and higher treatment expenses. The management of diseases is made more difficult by the scarcity of efficient substitute treatments, which frequently calls for the use of vital antimicrobials that are also necessary for human medicine.

Furthermore, food items, environmental channels, and direct animal-human interaction can all transfer resistant infections and resistance genes, increasing the danger of zoonotic transmission and compromising the efficacy of antibiotics in a variety of industries. This interrelated burden emphasizes the critical need for immunological and preventative measures that lessen reliance on antibiotics and protect the health of humans and animals within the One Health paradigm.

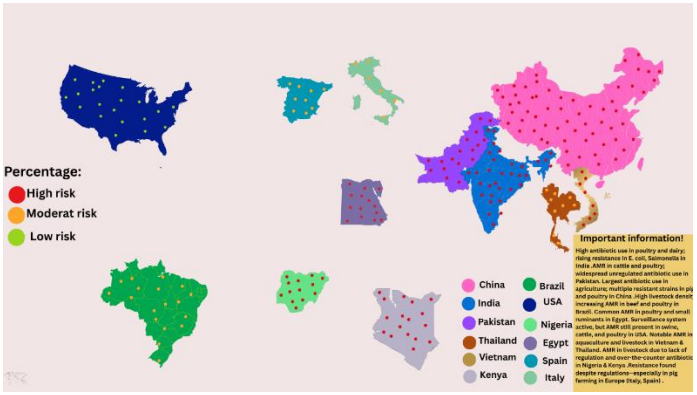

Figure 1: Geographic hotspots of veterinary AMR cases

Sixty percent of all human diseases are zoonotic (estimated in L.H. Taylor et al., 2001). Today, the emerging and re-emerging zoonotic diseases have posed a serious concern to the human well-being, as in the recent case of pig originated H1N1 influenza A pandemic in 2009 and camel originated Middle East Respiratory Syndrome Coronavirus (C. Fraseret al.,2009) Zoonotic agents are the transmissible infectious agents leading to disease in man and at least one other vertebrate animal species, in which it replicated or is closely related. Additionally, outbreaks of zoonotic diseases have proved detrimental to local economies: not only imposing great financial stress upon affected human populations but also in an indirect and negative manner upon trade and commerce with richer consumer nations concerned about the possibility of the disease spreading into their population (Woolhouse M, Gaunt E 2007).

From the last two decades, rapid globalization in food trade has been contributing many diseases. Alongside such expansion, public concern about global dissemination of zoonotic diseases, food safety, animal health and welfare and environmental contamination is increasing. The safety of animal foods is closely associated with animal health and herd management, which are directly affected by the existence and accessibility of proper veterinary diagnostic and public health services (Delgado CM, 1999). Zoonotic and emerging animal diseases and trade globalization are driving the need for animal health surveillance systems at the same time as human and financial resources to support public veterinary services are declining in many countries globally. This restricts all aspects of veterinary services activity including observation and surveillance (Anon.,2000).

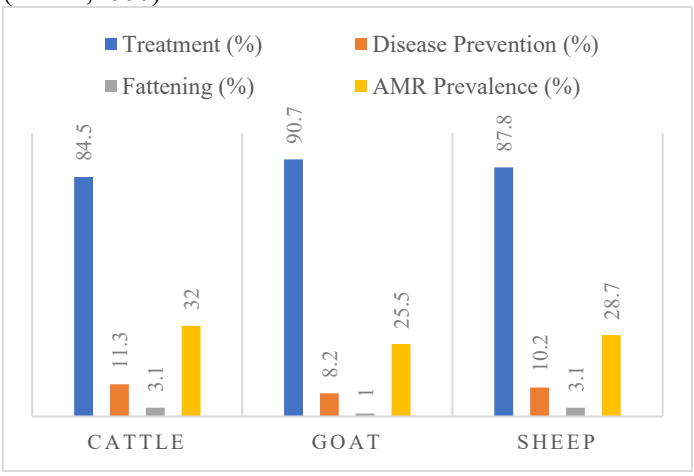

Figure 2: Prevalence of AMR in livestock species or antibiotic usage trends in veterinary sectors

3. THE ROLE OF VACCINE IN AMR MITIGATION

Vaccine (origin: Vaccinus, from the Latin word for cow) is an ancient concept described by Edward Jenner as the exposure of humans to cowpox virus to induce an immune response to the similar human smallpox virus, thus demonstrating the early integration of human and animal infectious disease sciences. Vaccination abolishes the human burden of zoonotic infectious diseases in themselves and their domesticated animals. Nevertheless, the

vaccinates in most cases are themselves the target, rather than the infecting, species, and few experimentally implanted examples of how it might be possible intervention strategy by vaccinating natural animals such as domesticated (One Health: A New Professional Imperative: AVMA One Health Initiative Task Force Report 2008) we need vaccines that not only stop disease from occurring in both humans and economically important animals who can be the source of infection but also break chains of transmission of infection in nature. Vaccines are now available to protect dogs against a few pathogens (Greene et al., 2001, Gaskell et al., 2002), and opportunities for the protection of dogs against additional infectious agents may arise as new methods for developing vaccines are developed. Furthermore, rabies imposes a major burden of morbidity from bites of rabid animals, many of which are severely disfiguring. Estimates of the incidence of bite injuries inflicted by suspect rabid dogs ranges from 40 to 288 cases/100,000 people (Zeynali et al., 1999, Cleaveland et al., 2002, Fèvre et al., 2005).

By preventing viral infections before they arise, vaccines significantly reduce the requirement for antibiotics in veterinary treatment and help mitigate antimicrobial resistance (AMR). Vaccination programs reduce the need for prophylactic and therapeutic antimicrobial medication in livestock and companion animals by improving herd immunity and reducing the frequency, severity, and spread of bacterial and viral diseases. The selection pressure that propels the development and dissemination of resistant infections is lessened by this decrease in medication exposure. Furthermore, within the One Health concept, vaccines can be developed to specifically target zoonotic or high-burden infections, improving animal productivity and health while also protecting human populations. Vaccines are an essential immunological method for encouraging responsible antimicrobial stewardship and bolstering long-term management of antimicrobial resistance (AMR) across interrelated animal, human, and environmental health systems. They are also affordable and sustainable preventive measures.

For infections that are spread predominantly through infectious pathogens excreted by infected members of a herd, herd resilience also includes further elements: the environmental burden of the pathogen, susceptibility to infection and the extent and duration of the period of infectiousness in those who do become infected. In the field of animal production, disease resilience has been described conditionally as the capacity of an individual animal, a herd (composed of animals) or a production unit (a set of herds) to maintain high performance even though challenged by a pathogen pressure (Bisset and Morris, 1996). Resilience is here more precisely defined as the ability to be invulnerable to the effects of infectious pathogens or the ability to return to the state before an infecting pathogen (after Colditz and Hine, 2016).

Infections in which herd immunity can play a role in shaping the risk of an infection among susceptible persons in a population, includes infections that are transmitted directly from person to person (e.g. measles, rubella, varicella) for which humans are, or important, reservoir of infection, (polio, malaria). There is probably no herd immunity (the infection is also not communicated from human to human) and humans are no important patient reservoir (examples:tetanus, rabies) pressure (Rousham, E. K et al., 2018) that in nature (Allen, H.K et al., 2018) is a process that takes relatively long for the evolution of bacterial AMR overuse of antimicrobials for almost 100 years has sped up this natural cycle very incredibly that makes it difficult to treat bacterial AMR effectively around the world.

The evolution and transmission of AMR is a complicated process resulting from the interaction of intrinsic determinants and extrinsic drivers. Apparently, the ARGs and MGEs combined and coexist in the bacterial chromosomes as the intrinsic determinant of ARGs (Yu, P., Dong, P et al.,2022) The MGEs are majorly consisted of plasmids, transposons, integrons, etc., which played determinant actions in the potential mobility of ARGs. Direct Factors: Selective pressures by chemicals in the ecological niches, including antimicrobials (including heavy metals and disinfectants), etc (Irfan, M. et al., 2022). The mediate factors are including social (national medicine policy, environmental protection policy, etc.), economical (intensive farming density, retail price of meat product, etc.), drug (antimicrobial price, desinfectant utilization mode of hospital infection, etc.), health (food hygiene, environment hygiene, etc.), climate (include temperature and humidity, pollution of environment, high wind, rain, etc.) factors.

The impacts of vaccines on AMR as a result of all these effects can be further enhanced by indirect protection or herd immunity (Fine PEM et al., 1993), which is generated when vaccinated persons are not infected or colonized and

do not transmit the pathogen to others. And in doing so not only can infections and drug-resistant infections and antimicrobial use be decreased among the vaccinees but also among their contacts.

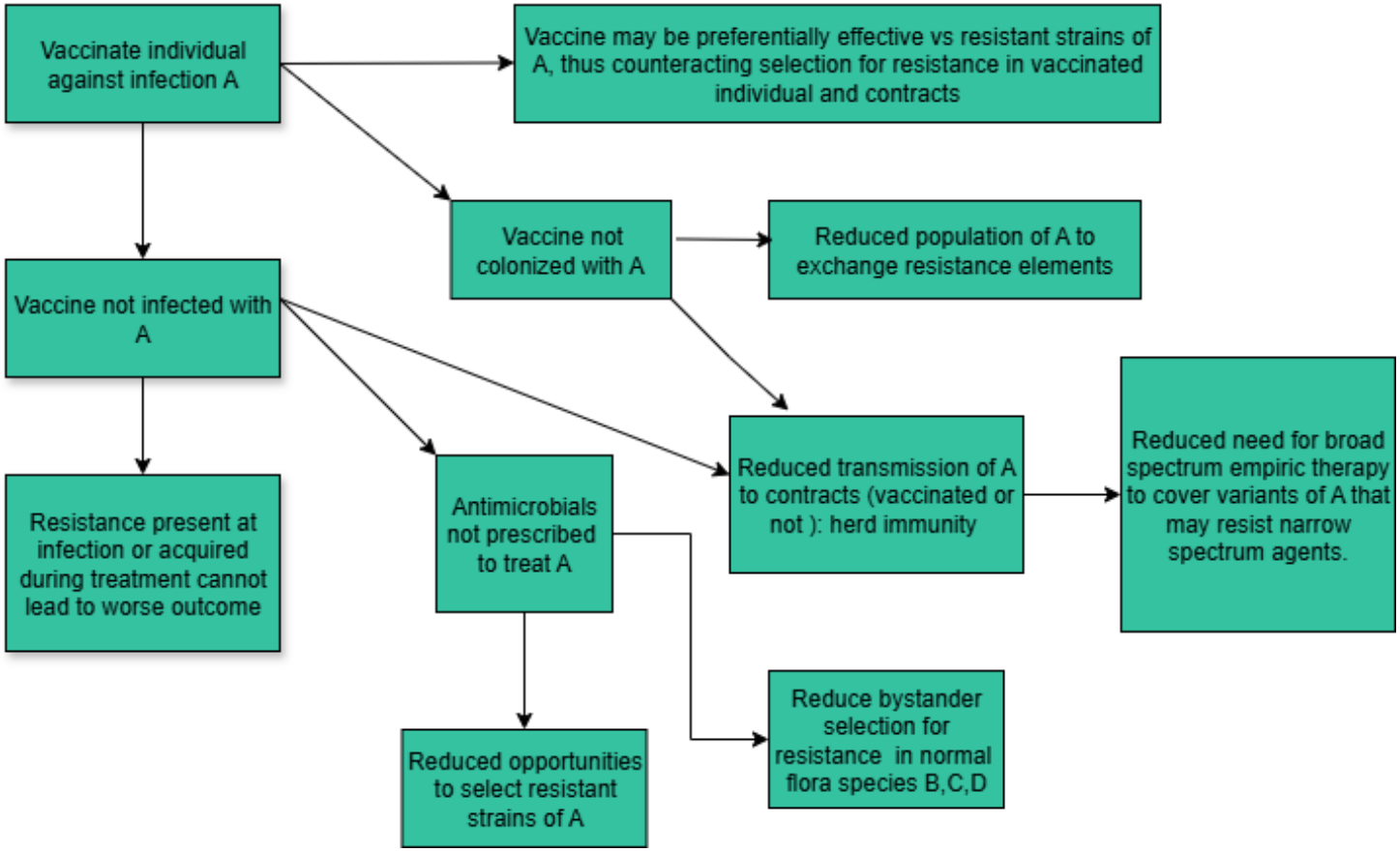
Vaccinate individual against infection A
Vaccine may be preferentially effective vs resistant strains of A, thus counteracting selection for resistance in vaccinated individual and contracts
Vaccine not colonized with A
Reduced population of A to exchange resistance elements
Vaccine not infected with A
Resistance present at infection or acquired during treatment cannot lead to worse outcome
Antimicrobials not prescribed to treat A
Reduced transmission of A to contracts (vaccinated or not): herd immunity
Reduced need for broad spectrum empiric therapy to cover variants of A that may resist narrow spectrum agents.
Reduced opportunities to select resistant strains of A
Reduce bystander selection for resistance in normal flora species B,C,D

Figure 3: Showing how vaccines reduce infection and antibiotic use

Development of safe and effective vaccines is one of the pressing challenges in human and veterinary medicine. Indeed, the development of new vaccines has become a process of empirical trial and error, with limited attention being given to theoretical considerations of the pathogenesis of, and immune response to, infectious diseases. It is important to determine the relevant pathway of each infection and build a vaccine that will induce the appropriate pathway. Because one pathway is naturally down regulating the other, the magnitude of immune activation must be tuned to achieve optimal defense. There have been a variety of human and animal vaccines since Pasteur's administration of the live attenuated (non-virulent) fowl cholera vaccine more than a century ago. Fears of the safety of vaccines have occasioned the production of inactivated (killed) or chemically detoxified (so-called toxoid) vaccines for most of the early vaccines The basic role is that the most effective route of vaccination is the route by which an person acquires the infection. Several pathways can be employed for vaccinating. They are the parenteral transcutaneous and mucosal mucus.

FJAR Falcons Journal of Advanced Research
ISSN: 3079-3319
Volume: 3,
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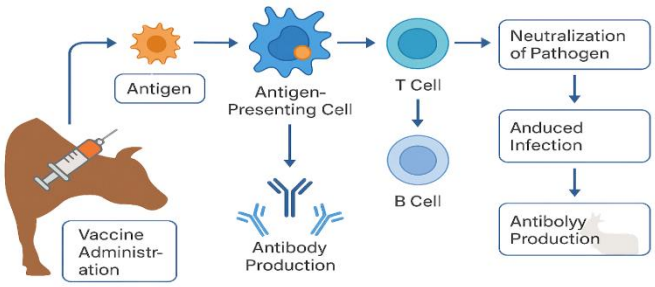

Figure 4: Immune response mechanism triggered by a veterinary vaccine

4. IMMUNOMODULATORS: ENHANCING INNATE IMMUNITY

In the context of veterinary and One Health frameworks, immunomodulators offer a promising means of boosting innate immunity and decreasing dependency on antibiotics in the fight against antimicrobial resistance (AMR). Immunomodulatory drugs enhance an animal's resistance to or speed of recovery from infections by stimulating or regulating the host's natural defensive mechanisms, in contrast to traditional antibiotics that target germs directly. Compounds such as cytokines, toll-like receptor agonists, probiotics, and plant-derived immunostimulants can strengthen barriers to infection, activate phagocytic cells, and promote balanced inflammatory responses, thereby decreasing disease susceptibility and severity. These strategies restrict the selection pressures that lead to the development of resistance by preventing infections or reducing their duration, which lowers the frequency and severity of antimicrobial treatments. Under the One Health paradigm, immunomodulators provide a sustainable, host-centered alternative as part of an integrated preventative strategy that promotes production, animal health, and more public health objectives.

Immunomodulators are compounds that are used to help improve the function of the immune system. The immune system is naturally armed with cells that can recognize and eradicate alien invaders, but it can become feeble without the aid of immunomodulators. The gut microbiota has a crucial effect on the immune system. Thus, while probiotics stuffed to improve the intestinal microbiota in immuno prevents (Zhao X et al.,2016). Innate immunomodulator plant polysaccharides can affect the acquired, adaptive and innate immune systems via interactions with leukocytes, monocytes, macrophages and B- and T-lymphocytes. It is immunomodulation, you're playing with the immune system and the ability to upregulate it or downregulate it. And limited for only one type of antigen (i.e. vaccine) immunopotentiation for the generation of immunity in body to one disease. Non-specific immunomodulation refers to a general immunity modification, which reflects alterations in the host reactivity to many antigens. Immunomodulation is one of the most alternatives to control the diseases with further benefits of enhancing the specific to vaccines.

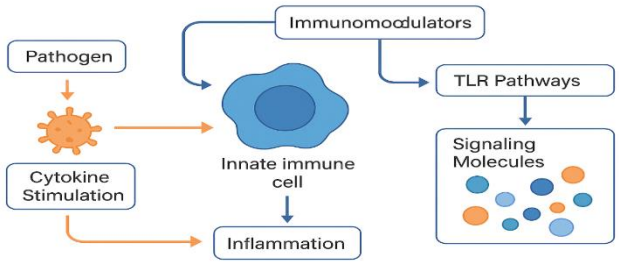

Figure 5: Innate immune system and where immunomodulators act (e.g., cytokine stimulation, TLR pathways)

Immunomodulation is a potential means of improving disease resistance without antibiotics to food animals.The most dynamic and rapidly progressing branches of immunomodulation is based on the phenomenon of trained immunity, where, following priming, innate immune cells are subjected to epigenetic reprogramming by remodeling of the chromatin architecture and the metabolic adaptation, which leads to increased or suppressed responses to subsequent stimuli (training or tolerance, respectively). Although several methods exist to control disease and antibiotic use in farm animals, still effective means of intervention have been missing for many infectious diseases of farm animals. One strategy to activate or sensitize (Kleinnijenhuis J et al., 2012) the innate immune system of a host for protection against infection is immunomodulation. Vaccines are potent immunomodulatory agents and how the adaptive immune system is engaged are familiar to infectious disease specialists. Innate immunomodulation in food animals is aimed at improving the immune status of the host and the resilience to diseases to improve animal wellbeing and production efficiency (Kollmann TR et al.,2017).

Immunomodulators are a vast class of agents with the ability to modify the immune response, either by stimulating or suppressing the immune system, that have been indispensable in therapeutic and prophylactic medicine. These agents are broadly classified as immunostimulants, immunosuppressants, immunoadjuvants, and biological response modifiers (BRMs) (Kumar et al., 2022). Immunostimulants (such as IL-2, BCG vaccine, levamisole) act by stimulating elements of the immune system (like macrophages and natural killer cells) and are popular in treating immunodeficiency states and cancers. In contrast, immunosuppressants such as cyclosporine, glucocorticoids and azathioprine, which act against T-cell proliferation or modulate inflammatory cytokines, are crucial in the treatment of autoimmune disorders and in decreasing the incidence of transplant rejection (Kumar et al., 2022). Immunoadjuvants, which are commonly used as vaccine components, facilitate antigen-specific responses by interacting with antigen-presenting cells and extending the duration of antigen exposure. BRMs facilitate immune reactions and may include monoclonal antibodies, and interferons, which are valuable in treating cancers and viral infections. The mechanism of action of these immunomodulators is multilevel, from the cellular signaling over the cytokine modulation to immune checkpoint interaction. Their uses are broad and, in addition to chronic infections and autoimmune diseases, cancer and vaccine adjuvants in both human and veterinary medicine applications can be considered already. Because of their wide therapeutic potential, their classification and mechanisms of action need to be well understood to be able to maximize their safe and targeted usage in clinic (Kumar et al., 2022).

Table 1: Common immunomodulators used in veterinary species

Immunomodulator	Type	Mechanism of action	Veterinary application	Species
Interleukin-2 (IL-2)	Cytokine	Stimulates proliferation of T cells and NK cells	Viral infections, cancer therapy	Dogs, cats, horses
Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)	Cytokine	Enhances differentiation and activity of macrophages and neutrophils	Immune recovery post-infection or chemotherapy	Dogs, cattle
β-glucans	Natural polysaccharide	Activates macrophages via pattern recognition receptors (e.g., Dectin-1)	Improves resistance to infections	Fish, poultry
Levamisole	Synthetic compound	Stimulates T-cell and macrophage activity	Parasitic infection control, general immunity	Cattle, sheep
Lactoferrin	Iron-binding glycoprotein	Binds iron to inhibit bacterial growth; modulates cytokine production	Mastitis treatment, gut health	Cattle, poultry
Toll-Like Receptor (TLR) agonists	Synthetic or microbial	Mimic pathogen-associated signals to activate innate immunity	Vaccine adjuvants, immune priming	Multiple species
Plant-derived compounds (e.g., Echinacea, Aloe vera)	Natural phytochemicals	Modulate cytokine production and enhance phagocytosis	Immune boosting supplements	Horses, dogs, poultry
Mycobacterium phlei extract	Bacterial derivative	Stimulates innate immunity and non-specific resistance	Respiratory infections	Cattle, horses
Probiotics (e.g., Lactobacillus spp.)	Microbial	Enhance gut immunity, modulate mucosal immunity	Gastrointestinal health	Poultry, ruminants
Zinc and Selenium	Trace elements	Support immune enzyme function, antioxidant defense	Immunity support, deficiency correction	All livestock and companion animals

Immunostimulants are a broad term to describe a very huge collection of naturally occurring and synthetic compounds that can stimulate immune response, and specifically innate immune mechanisms which stand the first line of defense against infections. Both the Toll-like receptor (TLR) agonists and microbial-derived products are powerful activators of the macrophages, dendritic cells, and natural killer cells (Shahbazi & Bolhassani, 2016).

Prevention and control of FADs are the common concern of all countries. The total benefits of better animal identification systems during FAD outbreaks are the sum of costs avoided due to improved animal identification systems. These advantages include preventing the spread of a FAD, facilitating rapid trace-back of infected animals, minimising production losses resulting from the presence of a disease, reducing the cost to Government of control, intervention and eradication and, in the final analysis, reducing potential trade losses (Carpenter T.E. & Howitt R et al.,1982) Epidemiology is a valuable new dimension and technique to elucidate and measure the interrelated risk factors generating disease. Meanwhile, health management or production medicine is defined as a comprehensive, preventive or performance-driven, database-using and economically structured system for preempting disease and promoting performance. Effective health management integrates animal productivity and disease prevention with the economic interests of owners and industry. Crucially , this approach also accounts for broader impacts on public health, food safety, animal welfare, and environmental stewardship.

5. PHAGE THERAPY: A TARGETED APPROACH

In veterinary medicine and the larger One Health framework, phage therapy is becoming a highly focused and novel strategy to fight antimicrobial resistance (AMR). Without interfering with the beneficial microbiota or applying the broad selective pressure that comes with traditional antibiotics, bacteriophages viruses that precisely infect and lyse bacteria provide a precise way to eradicate harmful bacteria. Because of its specificity, phage therapy is very useful in treating bacterial illnesses in livestock and companion animals that are resistant to many drugs. Furthermore, phages could change with their bacterial hosts, which may prevent resistance from developing over time. Phage therapy can improve therapeutic effectiveness while lowering the use of antibiotics, either by itself or in conjunction with immunological therapies or antibiotics. Phage-based therapies have great potential as a flexible and sustainable way to reduce antimicrobial resistance (AMR) in the environmental, human, and animal health, despite practical and regulatory obstacles.

Bacteriophages, or bacterial viruses, have life cycles that are closely dependent on the bacterial cells that they colonize. Because of their mode of action, which is based on their absence of a specific enzymatic system, bacteriophages cannot survive on their own outside a host cell. Phages are present across almost all natural ecosystems and have been widely detected in both human and animal hosts. Specifically, they colonize the respiratory and gastrointestinal tracts and the oral cavity and can even be isolated from systemic sources like serum and urine. They play a role in maintaining the homeostasis of natural ecosystems (Łusiak-Szelachowska et al., 2017).

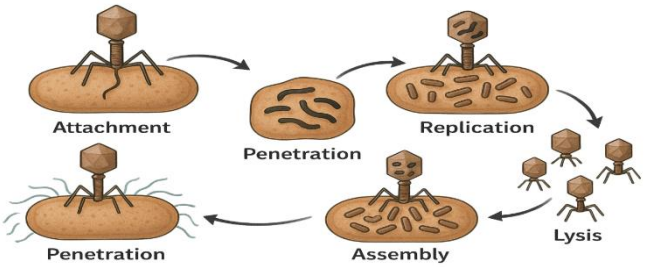

Figure 6: Lifecycle of a bacteriophage and how it attacks bacteria.

Bacteriophages, phages, are a group of viruses that infect and multiply in the bacterial cell, and their life cycle consists of an orderly sequence of events, including adsorption, injection, replication of virus component, assembly, and cell lysis. First, phages bind to receptors on the bacterial surface; it is an extremely specific event and determines the host specificity. Upon the attachment the phage injects its genetic material (DNA or RNA) into the host cell, while the protein coat remains outside (Sharma et al., 2017). Within the host, the phage genomic material takes over the bacterial machinery to reproduce its nucleic acids and to produce viral proteins. This is succeeded by the construction of fresh phage progeny in the bacterium. In the end, the most lytic phages encode enzymes (endolysins, holins, etc) that digest the cell wall and catastrophically destroy the cell, and progeny virions escape to infect other host cells (Sharma, Yamamura et al., 2017). Some phages, such as temperate phages, can integrate their genetic material into the chromosome of their host bacterium and continue to leave their DNA in silence until the phage is induced to make new particles. This bidirectional lifecycle makes bacteriophages not only bacterial killers, but also the genetic vectors that participate in horizontal gene transfer Expressed as antibacterials and horizontal gene transfer under certain circumstances (Sharma et al., 2017). The specificity and accuracy of these mechanisms is the inspiration for their use in phage-based therapies and other antimicrobial strategies.

FJAR Falcons Journal of Advanced Research
ISSN: 3079-3319
Volume: 3,
Issue:(01)
Nov 25 - Jan, 2026

Phage particle Phage particles are composed of nucleic acid (genetic material) and of proteins as the main structural matter of phages and with enzymatic characteristics. There are also filamentous phages, and icosahedral phages with tails, non-tailed phages, and numerous phages that have a lipoprotein envelope or that have lipids in the particle shell (Ackermann, 2006).

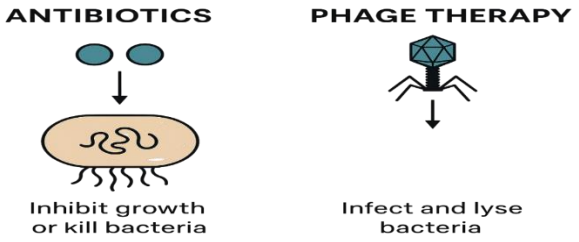

Figure 7: Comparing antibiotics vs. phage therapy mode of action.

Environmental conditions and phage resistance are the important aspects to be considered in phage therapy. Extrinsic factors affect the stability of bacteriophages. For long-term storage in solution or dry state, bacteriophages are kept at neutral pH (6–8). Phage replication is generally reduced at lower pH (4–6). In most cases, temperature influence on phage survival is low. Many of them can live at temperatures between 40 and 90 °C (Pirnay, J et al., 2008), and some phages, such as the one infecting Lactococcus, even can resist pasteurization temperature (Madera, C et al., 2004). There are several potential benefits for phage therapy in the treatment of bacterial infections. And they can do so even against bacteria that are resistant to them, as good murderers should. Mastitis is just one of the bovine diseases for which phage therapy has been suggested as a remedy. Metritis is an acute systemic illness of the cow in first three weeks postpartum and has been associated with adverse reproductive effects (Sheldon, I.M et al., 2009). The most overwhelmingly abused use of antibiotics, however, may be in livestock, which poses a major threat. Treatment of predominantly cattle and swine infections with phages has been proven to be successful (Dec M. et al., 2020). Lytic phage-infected bacteria cannot recover viability. Few, in contrast, are bacteriostatic only (thus potentially permitting the development of bacterial resistance) (LocCarrillo and Abedon 2011).

Implementing bacteriophages as clinical treatments present significant challenges. Standardized manufacturing and thorough characterization are essential prerequisites; these ensure that early phages trials can definitively establish safety and tolerability before progressing to efficacy studies. Ultimately, the clinical success of phage therapy depends heavily on the purity and stability of the final medicinal formulation. Phages would have to be developed on a large scale and under Good Manufacturing Practices (GMP) good practice validated by the regulators to be widely usable in clinical practice (Regulski, Champion-Arnaud and Gabard 2018).

6. PROBIOTICS AND GUT IMMUNITY

The gut microbiota, the most abundant symbiotic interfacing ecosystem with the host, has been demonstrated to exert crucial effects on the preservation of gut homeostasis. The microbiota-companying in the gut ble4-forther(gut-GM) in animals is closely associated at relevance to hosts, diets, and gut mucosal and immune system. The mammalian gut is the largest immune organ in the body and contains cells of both nonhemopoietic (epithelia cells (2), pencells (3), goblet cells (4)) and hemopoietic origin (macrophages (5), dendritic cells (3), T cells (6)), and is also a residence of trillions of microbes collectively known as the microbiota (7).

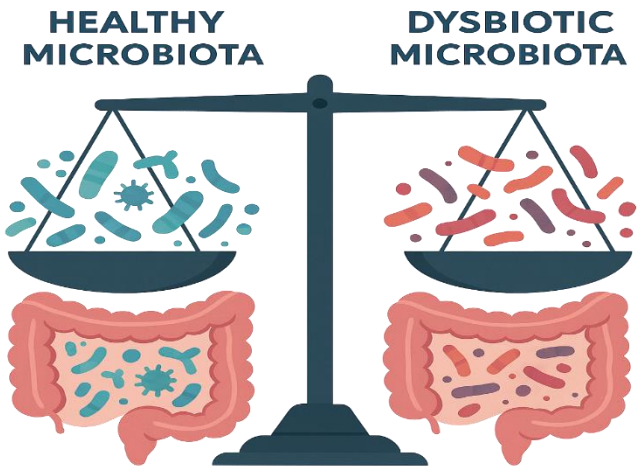

Figure 8: Balance of healthy vs. dysbiosis microbiomes.

The complex gut microbiome is not an inert organ, or a set of ‘passenger’ microorganisms, however, the intestinal community is an active ecosystem that forms an integral part of vertebrate immunity and physiology. Gut microbiota offers several health benefits such as nutrient metabolism and absorption, play in the construction of the host intestinal epithelial barrier, in the development and function of the host immune system, and in the competition with

pathogenic microbes to avert their harmful expansion (Maslowski KM et al., 2010). In veterinary and One Health contexts, probiotics are a supportive immunological therapy for reducing antimicrobial resistance (AMR) and are crucial for bolstering gut immunity. Probiotics improve the gut's natural barrier function and competitively prevent the colonization of pathogenic and antibiotic-resistant bacteria by fostering a diverse and balanced intestinal microbiota. By boosting mucosal immunity, controlling inflammatory pathways, and activating innate immune cells, they also alter both local and systemic immunological responses. It has been demonstrated that probiotic supplementation enhances growth performance and disease resistance in animal production, lowering the demand for growth-promoting and preventive antibiotics. In line with One Health's objectives to prevent the spread of resistance among animals, people, and the environment, probiotics help reduce antimicrobial dependency and promote sustainable animal health management through their combined impact on immune modulation and microbiome stability.The GM is known as the community of microorganisms residing in a specific environment along the GI tract, which consists of bacteria, fungi, protozoa, archaea and yeasts. Because more than 98% of nonhost derived genetic sequences in the gut are bacteria, the term and the majority of studies on this topic have focused on bacteria in the GI tract (Jandhyala SM et al., 2015).

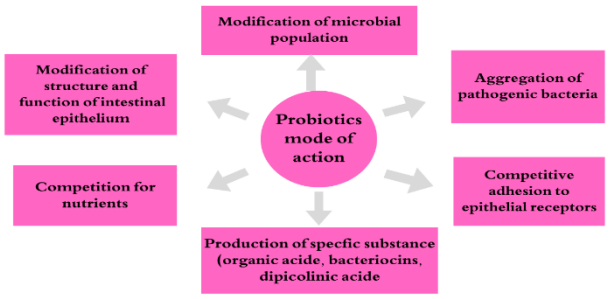
Modification of microbial population
Modification of structure and function of intestinal epithelium
Aggregation of pathogenic bacteria
Probiotics mode of action
Competition for nutrients
Competitive adhesion to epithelial receptors
Production of specfic substance (organic acide, bacteriocins, dipicolinic acide

Figure 9: Explaining the mechanism of how probiotics support immunity.

Probiotics are described as live microorganisms that when administrated in adequate amounts confer a health benefit on the host (Nomoto K et al., 2005). Probiotics used in a sick patient, optimally, derived from the species of the sick patient and were nonpathogenic, resistant to gastric acid and intestinal enzyme digestion, adherent to the intestinal epithelium, and able to modulate the host immune response (Dotan I et al.,2005). In Refeld et al. (2020), the modes of action of probiotics—termed immunobiotics because of their immunomodulatory effects—have been reviewed considering their application to the veterinary field. The authors point out that immunobiotics exert their effects mainly by the modulation of the host response and intestinal homeostasis. The probiotics interact with gut associated lymphoid tissue (GALT) and primes innate and acquired immunity. Some of the key mechanisms are the activation of macrophages, dendritic cells and natural killer (NK) cells and stimulation of the production of cytokines such as interleukins and interferons, important in signal and immune functions. Moreover, immunobiotics regulate the expression of Toll-like receptors (TLRs), key receptors to recognize pathogen microorganisms and trigger immune responses. Also, they are involved in regulating the Th1/Th2 immune response and in promoting the function of the intestinal barrier through tightening the tight junctions and mucin production to block the adhesion and invasion of pathogens. These pleiotropic activities justify the use of immunobiotics not only in gut health promotion but also in infection control and general increased animal immunity (Refeld et al., 2020). Probiotics are available in multiple formulations - pelleted feed, fermented feed, capsules, paste, powder, and granules. It has recently been suggested that inactivated" bacteria also have the probiotic effect, namely, that of the immune-modulating function and should be included in the category of probiotics in the broad sense (Tsukahara et al. 2005). probiotic organisms with relatively strong power of adhesion to the intestinal mucosa, will suppress strongly the adhesion of pathogens (Fuller 1991).

Embryo handling and post hatch immuno-physiology of the gastrointestinal (GI) tract: In modern broiler production complexes, several enhanced stressors such as feed changes or imbalances, transportation, in hatchery processing and high stocking densities can occur and all of these factor negatively influence upon the post hatching colonization of the GI tract by pathogenic enteric bacteria due to compromised immune system, which in turn affects the birds health and the poultry food safety (Pinchasov Y et al.,1993). The endogenous intestinal microflora can oppose pathogens by competition for adhesion sites and nutrient substrate and generation of toxic or immune-stimulatory metabolites (Paravez et al., 2006).

7. INTEGRATIVE STRATEGIES FOR SUSTAINABLE AMR CONTROL

Good hygiene, use of bio-security measures, vaccination and other strategies to boost immunity are used as preventive and control measures in public health in order to reduce and control the impact of disease. Illustrating these measures and their possible effect in diminishing AMR, World Bank (World Bank. Collaboration to overcome superbug infections: Addressing the global threat of antibacterial resistance. 2019) coined the terms AMR-sensitive and AMR-specific to refer to interventions that contribute indirectly or directly to AMR reduction, respectively. For instance, interventions that reduce the infectious burden on human health (eg, water, sanitation, hygiene; WASH), while not directly addressing AMR, are considered important for AMR strategies because there is an opportunity to indirectly address AMR and generate co-benefits. To address the public health impact of AMR a collective response from health services, agriculture, environment management and policy frameworks is necessary. As AMR is an issue that impacts human, animal and environmental health, the approach should be based on the principles of one health and planetary health, considering the inter-relatedness of these systems.

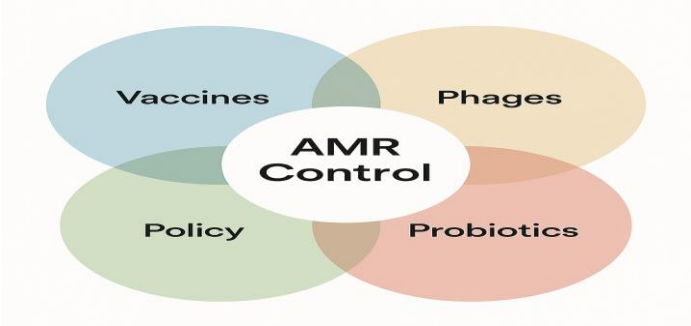

Figure 10: Systems showing integration of vaccines, phages, probiotics, and policy in AMR control.

In order to decrease reliance on antibiotics in veterinary and One Health systems, integrative techniques for sustainable antimicrobial resistance (AMR) control place a strong emphasis on the coordinated use of immunology, management, and stewardship approaches. Combining vaccinations, immunomodulators, phage therapy, probiotics, and enhanced biosecurity measures instead of depending on individual therapies results in a multilayered defense that reduces the spread of pathogens, boosts host immunity, and avoids infections. Policies governing the safe use of antibiotics, surveillance programs, and improved farm management techniques including stress management, nutrition, and hygiene all help to make animal populations healthier and more robust. Integrative approaches provide a sustainable way to reduce selective pressure for resistance while preserving animal productivity, food safety, and public health within the interconnected One Health framework by concurrently addressing disease prevention, treatment options, and environmental factors. Also, community activation and broadcasting of the value of responsible AMU is required to induce behavioral change leading to unnecessary prescriptions (Godman, B et al.,2021). Not only are research and innovation important for developing new AMAs and novel interventions, it is also essential for discovery of new non-antibiotic agents and alternative interventions for such research and innovation to thrive. Although vaccines and bacteriophage therapies are promising approaches to reduce dependency on conventional antibiotics, bacteriocins, particularly bacteriocins synthesized by bacteria are also identified as a very promising alternative option that require exploration (Gupta, R et al., 2022) In addition, strengthening surveillance networks worldwide will help to better monitor trends in AMR and to respond timely to AMR threats (Aijaz, M et al., 2023).

Educational programs directed toward both healthcare providers and the lay public are essential for promoting responsible antibiotic use. Studies have shown that such interventions can result in marked reductions in antibiotic prescribing (Velden et al., 2013; Zetts et al., 2020). Legislation in veterinary medicine should only allow the use of antibiotics on veterinary prescription and eliminate the use of antibiotics as growth promoters in animals (Wilkinson et al., 2018). Countries should exchange surveillance data, best practices, and approaches to the regulation of, and resistance to, antibiotics. International organizations like WHO and FAO are crucial in the AMR agenda setting, through creating settings where interventions can be standardized globally (Alanazi, 2023; Gerber et al., 2013).

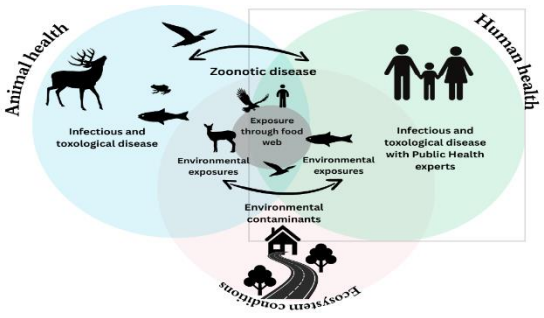

Figure 11: One Health Model Diagram (animal-human-environment link).

The WHO, and others, are formulating guidelines on the growing problem of antimicrobial resistance (WHO 2015). They are calling for One Health participation of all parties in all disciplines because – no one will be spared of AMR irrespective of our state of health. However, effective implementation of these plans has been difficult due to the battle for resources to properly support these plans, this was reported by WHO in 2019 (WHO Putting plans into action for antimicrobial resistance (AMR) 2019). The financial limitations do not allow the full implementation of strategies to alleviate AMR at a worldwide level. The consequences of AMR are not confined to public health but extend to global socio-economic development.

Innovative approaches to tackling AMR cut across healthcare settings and need varied responses, such as public education and awareness programs, improved infection control, and the incorporation of antimicrobial stewardship in clinical care (Atif & Tufail, 2022; Pakyz et al, 2014). Surveillance and reporting mechanisms are essential for follow-up of antibiotic consumption and resistance trends and for rapid decision making (Karavolias et al, 2018). The linkage of an education to policy, stewardship programs and internationalization is central in a bid to minimize these risks around AMR and therefore effectively protect public health for the generations to come (Babarinde, et al, 2018).

8. CONCLUSION

To sum up, combating antimicrobial resistance (AMR) in veterinary medicine necessitates a change in approach from the use of traditional antibiotics to immune-centered, sustainable, and preventive methods that complement the One Health paradigm. Effective substitutes that improve host defenses, lower illness incidence, and restrict the selective pressures that lead to the evolution of resistance are provided by immunological therapies, such as vaccines, immunomodulators, phage therapy, and probiotics. These methods offer a thorough means to ensure treatment efficacy for future generations when combined with enhanced biosecurity, ethical antimicrobial management, and coordinated surveillance across the animal, human, and environmental sectors. Adopting such diverse approaches not only safeguards agricultural output and animal welfare but also makes a substantial contribution to international public health initiatives aimed at containing and lessening the escalating threat of AMR.

Veterinary immunology is a critical and future-oriented way of addressing the investment of the impending issue of antimicrobial resistance (AMR). These strategies equally minimize the use of antibiotics by strengthening the host immune response using vaccines, immunostimulants, probiotics and phage therapy, whilst effectively preventing and controlling the infection diseases. In contrast to the selective pressure by antibiotics that lead to resistance, the immunological interventions induce resilience to disease developing in animals, but they do not promote resistance. They are instrumental in protecting animal health and animal productivity but also are important in preserving the effectiveness of the current use of antimicrobials, which is part of the solution to AMR.

Furthermore, the application of these measures in a One Health context guarantees a comprehensive plan of action, since human, animal and ecological health cannot be separated. To be successfully implemented, the approaches based on immunology should be promoted, alongside the work of strong surveillance systems, specific investigations, awareness of people, and evidence-based veterinary policies. To put these innovations into practice, it is required to bring veterinarians, researchers, farmers and policymakers together. Since the problem of AMR continues increasing around the world, the introduction of immunological frontiers into veterinary practice is a lasting and scientifically valid option, a necessity to warrant animal health, food security, and human health at global level.

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